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Review

Promoting Health and Longevity through Diet: From Model Organisms to Humans

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Reduced food intake, avoiding malnutrition, can ameliorate aging and aging-associated diseases in invertebrate model organisms, rodents, primates, and humans. Recent findings indicate that meal timing is crucial, with both intermittent fasting and adjusted diurnal rhythm of feeding improving health and function, in the absence of changes in overall intake. Lowered intake of particular nutrients rather than of overall calories is also key, with protein and specific amino acids playing prominent roles. Nutritional modulation of the microbiome can also be important, and there are long-term, including inter-generational, effects of diet. The metabolic, molecular, and cellular mechanisms that mediate both improvement in health during aging to diet and genetic variation in the response to diet are being identified. These new findings are opening the way to specific dietary and pharmacological interventions to recapture the full potential benefits of dietary restriction, which humans can find difficult to maintain voluntarily.

Introduction

The discovery that aging can be ameliorated by dietary, genetic, and pharmacological interventions has opened up the prospect of a broad-spectrum, preventive medicine for aging-related diseases (Table 1) (Fontana et al., 2014; Goldman et al., 2013; Partridge, 2010). Single-gene mutations that extend animal lifespan can ameliorate natural, age-dependent loss of function (Metaxakis et al., 2014; Stein and Murphy, 2012) and the pathology of aging-related diseases, including neurodegeneration (Cohen et al., 2009; Killick et al., 2009; Menzies and Rubinsztein, 2010; Pinkston-Gosse and Kenyon, 2007; Stöhr et al., 2013). Furthermore, laboratory animal models of slowed aging, naturally long-lived species such as the naked mole rat, and some humans that achieve the age of 100 have all demonstrated that a long life is not inevitably associated with late-life disability and disease (Ikeno et al., 2006; Edrey et al., 2011; Ailshire et al., 2014). Recent work has shown that specific dietary interventions can also promote long life and healthy old age.

Dietary restriction (DR), implemented as chronic and coordinate reduced intake of all dietary constituents except vitamins and minerals, was first shown 80 years ago to extend lifespan in rats. DR in both rats and mice improves most aspects of health during aging (Fontana et al., 2010a; Ikeno et al., 2006; Maeda et al., 1985). Exceptions include resistance to infection and wound healing. However, these conditions rapidly improve with re-feeding, and DR animals can then outperform controls (Kristan, 2008; Hunt et al., 2012). DR can produce substantial benefits with, for instance, ~30% of DR animals dying at old ages without gross pathological lesions, compared with only 6% of ad-libitum-fed controls (Ikeno et al., 2006). DR started in young, adult Rhesus monkeys greatly improves metabolic health; prevents obesity; delays the onset of sarcopenia, presbycusis, and brain atrophy; and reduces the risk of developing and dying of type 2 diabetes, cancer, and cardiovascular disease (Colman et al., 2014; Mattison et al., 2012).

In humans, severe food restriction without malnutrition results in many of the same physiological, metabolic, and molecular changes associated with DR in animals, including less age-associated myocardial stiffness and autonomic dysfunction, lower core body temperature, and downregulation of the *pi3k/akt/foxo* and inflammatory pathways in skeletal muscle (Cava and Fontana, 2013; Mercken et al., 2013). Furthermore, humans voluntarily undertaking long-term DR score lower than controls on multiple risk factors for cardiovascular disease and cancer (Fontana et al., 2010b). In short-term, randomized clinical trials in aging humans, DR improves several markers of health (Heilbronn et al., 2006; Fontana et al., 2010b). However, severe DR with adequate nutrition (i.e., consuming at least 100% of the RDI for each essential nutrient) is not an option for most people because it is difficult to practice and sustain and, with inadequate nutrition, can increase the risk of impaired menstrual and reproductive function, osteoporotic bone fractures, anemia, and cardiac arrhythmias (Fairburn and Harrison, 2003). Dietary interventions that avoid unrealistic levels of self-deprivation, and pharmacological interventions that recapture beneficial effects of DR, are therefore important goals to improve human health during aging.

Table 1. Interventions Extending Mean and/or Maximal Lifespan in Wild-Type Mice Fed Normal Chow

	Max Lifespan	Mean Lifespan	Main Mechanism of Action
Dietary Interventions			
Calorie restriction	yes	yes	↓ nutrient-sensing pathways
Intermittent fasting	yes	yes	↓ nutrient-sensing pathways
Protein restriction	no	yes	↓ nutrient-sensing pathways
Methionine restriction	yes	yes	↓ nutrient-sensing pathways
Tryptophan restriction	yes	yes	↓ nutrient -sensing pathways
Physical Exercise Interventions			
Endurance exercise	no	yes	↑ insulin sensitivity; ↑ AMPK ?
Genetic Interventions			
Ames and Snell dwarf	yes	yes	↓ nutrient-sensing pathways
GH receptor KO	yes	yes	↓ nutrient-sensing pathways
IGF-1 R KO	yes (in F)	yes (in F)	↓ nutrient-sensing pathways
Klotho TG	yes (in M)	yes	↓ nutrient-sensing pathways
Fat Insulin Receptor KO	yes	yes	↓ nutrient-sensing pathways
Insulin Receptor Substrate 1 KO	yes (only F)	yes (only F)	↓ nutrient-sensing pathways
Brain IRS-2 KO	yes	yes	↓ nutrient-sensing pathways
PAPP-A KO	yes	yes	↓ nutrient-sensing pathways
Ribosomal S6 protein kinase-1 KO	yes (only F)	yes (only F)	↓ nutrient-sensing pathways
FGF-21TG	yes	yes	↓ nutrient-sensing pathways
miR-17TG	?	yes	↓ nutrient-sensing pathways
DGAT1KO	yes (only F)	yes (only F)	↓ nutrient-sensing pathways
p66shc KO	yes	yes	↓ growth factor-mediated signaling
ATG5 TG	yes	yes	↑ autophagy
Type 5 Adenylyl Cyclase KO	yes	yes	↓ β-adrenergic signaling
Angiotensin II type 1 receptor KO	yes	yes	↓ angiotensin receptor signaling
Catalase targeted to mitochondria TG	yes	yes	↓ oxidative stress (mitochondrial)
Ink4/Arf-TG/TG	no	yes	↓ mitogenic over-stimulation and cell proliferation
C/EBP β/β	yes	yes	↑ mitochondrial biogenesis in white fat cells
Mclk1KO	yes	yes	↓ age-dependent loss of mitochondrial function
Hcrt-UCP2 TG	no	yes	?; ↓ core body temperature
Macrophage migration inhibitory factor KO	yes	yes	↓ inflammation; ↓ insulin pathway
E-DNIκB TG	?	yes	↓ inflammation; ↓ insulin pathway
PKA RIIβ KO	yes	yes	↓ IGF signaling?
RasGRF1 KO	yes	yes	↓ nutrient-sensing pathways
Sirt6 TG	yes (only M)	yes (only M)	↓ nutrient-sensing pathways (IGF)
Brain-specific Sirt1 TG	yes (only F)	yes	↑ mitochondrial function via Sirt1/Nkx2-1/Ox2r
TRPV1 pain receptor KO	yes (only F)	yes	modulation of CRTC1/CREB activity
Pharmacological Interventions			
Rapamycin	yes	yes	↓ nutrient-sensing pathways (mTOR)
Acarbose	yes	yes	↓ IGF signaling and ↑ FGF-21
Metformin	no	yes	↓ nutrient-sensing pathways (AMPK)
Aspirin	no	yes (only M)	↓ inflammation
Nordihydroguaiaretic acid	no	yes (only M)	↓ inflammation and oxidative stress
Green tea extract	no	yes (only F)	↓ oxidative stress
17α-Estradiol (non-feminizing estrogen)	no	yes (only M)	? non-genomic actions
Methylene Blue	no	yes (only F)	↑ mitochondrial function
Metoprolol	no	yes (in M)	↓ β-adrenergic receptor signaling
Nebivolol	no	yes (in M)	↓ β-adrenergic receptor signaling

DR increases healthy lifespan in many shorter-lived organisms, including budding yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, and the fruit fly *Drosophila melanogaster* (Figure 1). The experimental tractability of yeast and invertebrates facilitates discovery of the—often evolutionarily conserved—mechanisms through which genetic and environmental intervention improve health during aging. The mechanisms mediating the health benefits of DR are not fully

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